M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: February 11, 2000

To: Dockets Management Branch (HFA-305)

From: Melissa Lamb
Office of Generic Drugs

Subject: In Vivo/In Vitro BE of Inhaled Products:
A Follow-up from the AAPS/FDA/USP
June Workshop: Roundtable

This memorandum forwards overheads of a presentation to the Dockets Management Branch for inclusion in Docket 90S-0308. The following is information on the presentation for the Docket records:

Title of Presentation: Documentation of Bioequivalence (BE) of Inhaled Drugs for Local Action: An FDA View

Presented for: New Orleans, LA

Date Presented: 11/16/99

Presented by: Wallace P. Adams, Ph.D.

Number of Pages: 28

Melissa Lamb

Attachment

90S-0308

M677

Documentation of Bioequivalence (BE) of Inhaled Drugs for Local Action: An FDA View

In Vivo/In Vitro BE of Inhaled Products:
A Follow-Up from the AAPS/FDA/USP
June Workshop: Roundtable

New Orleans, LA
16 November 1999

Wallace P. Adams, Ph.D.
Office of Pharmaceutical Science
CDER/FDA

HTTP://WWW.FDA.GOV/CDER/GUIDANCE/

Guidance for Industry

Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Wallace P. Adams (301) 594-5651 (CDER).

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Acknowledgments

- Office of Pharmaceutical Science
- Office of Generic Drugs
- Office of Clinical Pharmacology and Biopharmaceutics
- Division of Pulmonary Drug Products
- Division of Testing and Applied Analytical Development
- Division of Product Quality Research
- Quantitative Methods and Research Staff
- Thomas Jefferson University/Biostatistics Section

Draft Guidance Coverage

- Bioavailability (BA) Measurement
  - May be noncomparative
  - Characterization (benchmark) studies
  - PRODUCT QUALITY BA ONLY
  - Additional PK/Bio studies are not covered
- Bioequivalence (BE) Establishment
  - Comparative studies
- Covers locally acting drug products only

Locally Acting Drug Products (LADP)

The BA and BE Challenge:

Delivery to sites of action does not occur primarily after systemic absorption, hence

Pharmacokinetic studies are inadequate to fully document BA and BE

Approaches to Measure BA and Establish BE

- Pharmacokinetic
- Pharmacodynamic
- Clinical
- In vitro

BA and BE Concepts for LADP

- Local delivery
  - relates to efficacy
- Systemic exposure
  - relates to safety
  - may also relate to efficacy
    - e.g., levocabastine nasal spray

General BA and BE Approach

- Formulation equivalence (BE):
  - Q1 (excipients qualitatively the same)
  - Q2 (excipients quantitatively the same)
- Functional comparability of devices (BE)
- Solutions
  - In vitro BA and BE
- Suspensions
  - In vitro BA and BE
  - In vivo studies (two)

In Vitro BA and BE Data

- Apply to all aerosols and sprays
- Considered to be more sensitive indicators of differences in drug delivery to nasal sites than are clinical data
- Confidence intervals for comparative data of selected in vitro BE measures
- Statistics under development for the selected in vitro BE measures

In Vitro BA and BE Data: Specific Tests

- Dose or spray content uniformity through container life
- Droplet size distribution
- Drug particle size distribution
- Spray pattern and plume geometry
- Priming and repriming
- Tail off

In Vivo BE Data

- LOCAL DELIVERY based on clinical study
- SYSTEMIC EXPOSURE based on PK study, or
- SYSTEMIC ABSORPTION based on PD or clinical study
- In vivo data requested for suspension formulations only

Clinical Study for Local Delivery

- BE (NDA):
  - may use the same comparative studies used to establish S and E of the drug product
- BE (ANDA):
  - Three suggested clinical BE study designs
- Sensitivity based on dose-response

Systemic Exposure or Systemic Absorption: Which is Preferred?

- Preferred study:
  - PK study in healthy subjects
- Alternative when PK not feasible:
  - PD or clinical study in healthy subjects

Emphasis on In Vitro Data for Establishing BE

- Clinical studies are highly variable and relatively insensitive to product differences
- *Therefore*
- BE studies with PD or clinical endpoints will not be sufficient in the event of in vitro BE studies that fail to meet the criteria

FDA Draft Nasal BA/BE Guidance

- Posted to FDA's website
  - 2 June 1999
- Fed. Reg. Notice of Availability
  - 24 June 1999
- Close of Public Comment Period
  - 22 September 1999
- 14 Submissions to the Docket (as of 26 Oct 1999)
  - innovator firms
  - generic firms
  - trade associations
  - instrument manufacturer

Observations on Public Comments

- Comments reflect a diversity of views
- Comments are highly valuable to revision of the draft
- Comments must be reviewed and evaluated by the FDA OINDP Working Group members
- Observations at this Roundtable are the personal opinions of the speaker only

Selected Comments: Docket # 99D-1738

Draft BA and BE Guidance for Nasal Aerosols and Nasal Sprays for Local Action

(June 1999)

In Vitro and In Vivo Testing

- Both in vitro and in vivo testing is supported
  - in vitro methods only are applicable to solution formulations if Q_1, Q_2 and CCS recommendations are met
- Acceptable in vitro data, and limited or no in vivo studies, are needed for solution or suspension formulations meeting Q_1, Q_2 and CCS recommendations

Q_1 and Q_2

- Products should be qualitatively the same (Q_1) and quantitatively essentially the same (Q_2)
- The Q_1 and Q_2 recommendation is overly restrictive
- The Q_1 and Q_2 recommendation should not be required for suspension formulations.
  - The clinical study should determine BE

Container/Closure System

- For solution formulations, in vitro methods can be relied on only if Q_1 and Q_2 and CCS similarity are met
- The reference product may have a proprietary pump
  - A different pump may exhibit differences in droplet size, spray pattern, etc.
- If the dose, PSD, etc., are the same, then similar actuator design is not necessary

Priming and Tailoff

- Priming and repriming data should be required for an ANDA
- It may not be possible to attain prime within the labeled number of actuations of the reference product.
  - Accommodate differences in the labeling
- Tailoff
  - a labeling and CMC issue, not BA/BE
  - of questionable value, as the product should not be used past the labeled number of actuations

Particle Size Distribution - Laser Diffraction and Microscopy

- Both methods are of limited accuracy, and provide supportive BE data only
- Microscopic drug PSD methodology cannot be acceptably validated - do not request the data
- Laser diffraction data at three distances and different delay times is excessive
- D90 and D10 data are highly variable (up to 100% CV for D90)

Spray Pattern

- Testing in an unconstrained environment is an indirect measure of reproducibility
  - of uncertain clinical relevance as the nasal cavity is a confined airspace
- For mcg amounts of drug, a drug specific visualization technique may not be possible
- Variability in ovality ratio (D_{max}/D_{min}) is lower than variability in either D_{max} or D_{min}
  - confidence intervals on the ratio only are recommended

In Vivo Local Delivery

- Clinical studies are needed to establish therapeutic equivalence
- Dose-response should be documented in a BE. What if a dose-response relationship cannot be shown?
- The study should not include a dose-response study
  - D-R is not required in other BE studies with clinical endpoints for ANDA's
- An imaging method may be useful for in vivo confirmation of equivalent delivery
- With uncertainty in PSD and relationship to target sites, are clinical studies conducted in SAR adequate to assure BE for all indications?

PK Systemic Exposure Study

- PD endpoints are recommended as secondary endpoints to complement PK data
- Conduct the PK or systemic absorption study as part of the clinical study for local delivery
- A PK study should document sensitivity by inclusion of a second dose of T or R
- At greater than labeled doses, product may be lost from the nasal cavity, resulting in nonlinear PK
  - A reliable estimate of systemic exposure may need to establish dose proportionality

Systemic Absorption Study

- The most clinically relevant method for determining HPA axis function is currently under discussion
- Bone growth suppression may be a more sensitive indicator of systemic corticosteroid exposure than is an HPA axis test
  - particularly relevant if product is labeled for pediatric use
  - particularly relevant if reference product has shown growth suppression or if the effect is unknown
  - a one-year growth study is recommended
- A PD study should document sensitivity by inclusion of a second dose of R and possibly T